PG Textbook of PEDIATRICS

This book is printed in 3 volumes

VOLUME 1
GENERAL PEDIATRICS, INTENSIVE CARE, AND NEONATOLOGY

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PSN Menon
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Rakesh Lodha

3rd Edition

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31.19 Dengue

Piyush Gupta, Aashima Dabas

Dengue infection results in an acute febrile illness, caused by four closely related virus serotypes of the genus *Flavivirus*, family *Flaviviridae*. Dengue virus is transmitted to humans mainly by the *Aedes aegypti* mosquito. The disease is characterized by a biphasic fever, and may be associated with hemorrhagic manifestations. In 10–20% cases, the patient develops shock because of plasma leakage into the third space. Worldwide, children younger than 15 years comprise 90% of patients with dengue fever. Dengue is one of the 20 diseases listed by the World Health Organization (WHO) under their 2021–2030 roadmap against Neglected Tropical Diseases (NTDs).

CLINICAL SPECTRUM

Dengue virus infection may be asymptomatic, lead to a benign illness, or present with severe manifestations. The WHO in 1997 classified symptomatic dengue virus infections in the following groups:

- Undifferentiated dengue fever
- *Dengue fever:* Defined as presence of fever of 2–7 days duration with any two of the following—myalgia, retro-orbital pain, headache, rash, and arthralgia
- *Dengue hemorrhagic fever* (DHF)*:* A patient is classified as DHF if following four criteria are met: (1) fever or history of fever in last 2–7 days; (2) bleeding tendencies—positive tourniquet test, petechiae, purpura, mucosal bleeds; (3) thrombocytopenia—platelet count <100,000/mm^3; and (4) hemoconcentration [defined as >20% rise in hematocrit (Hct)] or evidence of plasma leakage—pleural effusion, ascites or hypoproteinemia. The DHF was further graded in four stages **(Box 1)**.
- *Dengue shock syndrome* (DSS). All of the above criteria plus hypotension.

Later, it was realized that this classification was at times difficult to apply in clinical settings, was not able to categorize all patients with dengue, and was missing out cases with severe dengue. Also, dengue fever and DHF may not be continuum of same disease and may exist as separate clinical conditions. The WHO thus proposed a new classification for severity of dengue fever in 2009.

The WHO classification in 2009 had three severity categories—(1) dengue fever; (2) dengue fever with *warning signs*; and (3) severe dengue **(Fig. 1)**. It is important to note that children without warning signs can also develop severe dengue.

BOX 1: Grading of dengue hemorrhagic fever (WHO, 1997).

Grade I: Fever, nonspecific complaints, positive tourniquet test, and no spontaneous bleeds
Grade II: Spontaneous bleeds in addition to signs and symptoms of grade I
Grade III: Circulatory failure—cold clammy extremities and hypotension
Grade IV: Profound shock

- *Nonsevere manifestations* consist of a biphasic fever, generalized body ache, rash, and a positive *tourniquet test*. These may or may not be associated with warning signs.
- *Warning signs* should be detected by close observation of the patient, so as to institute early and aggressive therapy. These include—(1) abdominal pain or tenderness, (2) persistent vomiting, (3) clinical fluid accumulation (edema, pleural effusion, and ascites), (4) mucosal bleeds, (5) hepatomegaly by >2 cm, and (6) hemoconcentration as evidenced by increasing Hct with concomitant and rapid fall in platelet count.
- *Severe manifestations* include—(1) severe hemorrhage, (2) profound shock, and (3) multisystem involvement. Presence of any one of these three criteria is sufficient for making a diagnosis of severe dengue infection.

Expanded dengue syndrome is a term introduced in 2011, which refers to unusual and severe involvement of the liver, kidney, brain, or heart in association with dengue.

National Vector-borne Disease Control Program Nomenclature

Recently, the National Vector Borne Disease Control Program (NVBDCP) has accepted the revised WHO classification for dengue as shown in **Flowchart 1**. There may be asymptomatic subjects who may be tested positive for dengue. Among symptomatic patients, they can be classified into three categories—mild, moderate, and severe dengue.

GEOGRAPHICAL DISTRIBUTION

Global

Dengue fever is known in the tropical Southeast Asia and Western Pacific for more than a century. The hemorrhagic form was first recognized in Philippines in 1953. Subsequently, DHF was recognized in Thailand, India, Malaysia, Singapore, and Vietnam. In 1978, a big outbreak was reported from China resulting in 22,122 cases. In 1981, a large epidemic occurred in Cuba resulting in nearly 0.35 million cases of dengue fever. Out of these, 24,000 had DHF and 10,000 had DSS. Dengue has also been noticed in temperate regions of North America, Africa, and Mediterranean Europe.

As per current estimates, at least 100 countries are endemic for DHF and about 40% of the world populations (2.5 billion people) are at risk in tropics and subtropics. In 2010, 1.6 million cases of dengue were reported in the Americas alone, of which 49,000 cases were severe dengue. Recently, dengue has also been reported from Costa Rica, Mexico, France, Croatia, and Portugal. Incidence of dengue infections annually has almost doubled from 50 million to 96 million (2010) in last few years. A recent meta-analysis on data

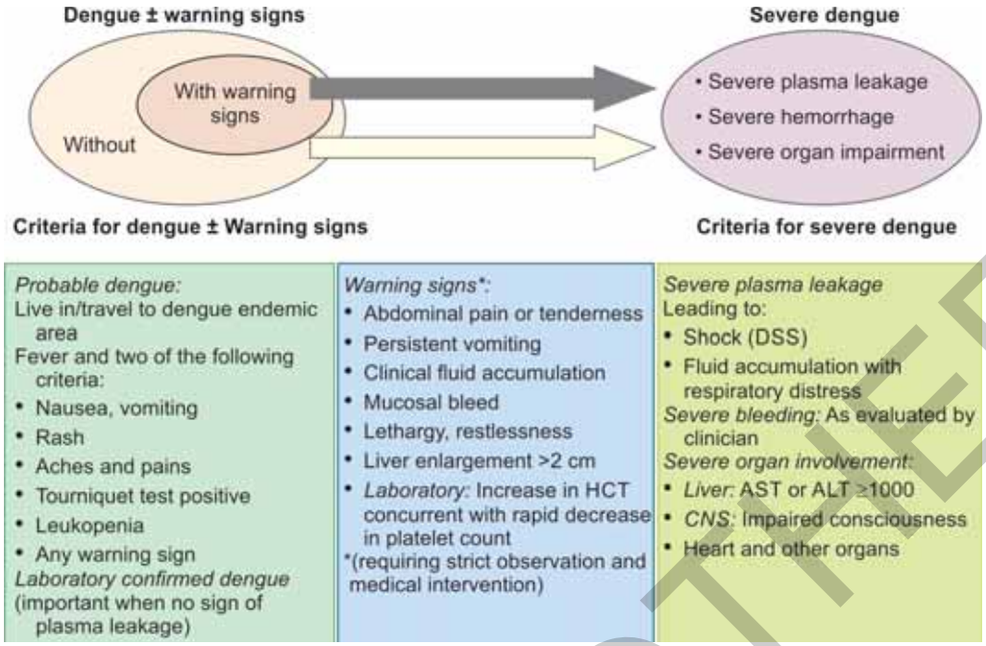


Fig. 1: Suggested dengue case classification and levels of severity.
(Hct: hematocrit; DSS: dengue shock syndrome; AST: aspartate transaminase; ALT: alanine transaminase; CNS: central nervous system)
Source: Reproduced with permission of the publisher from: Dengue, Guidelines for Treatment, Prevention Control. Geneva: WHO; 2009.

from 84 articles from 21 countries in sub-Saharan Africa showed an increase in the prevalence of IgM dengue antibodies suggesting that 10–14% population developed acute dengue infection in last 10 years and 25% of the population had elevated IgG suggesting history of exposure to dengue at some point in time. The pooled dengue virus RNA prevalence was 14% (95% CI: 12–16%), which reflected the poor vector control strategy in sub-Saharan Africa.

India

India alone accounted for almost 34% of global dengue burden by 2010. The National Dengue Day was observed on 16th May 2016. Disease is prevalent throughout India in most of the metropolitan cities and towns and is endemic in 18 out of 35 states. Outbreaks have also been reported from rural areas of Haryana, Maharashtra, and Karnataka. Recent trends in transmission have shown occurrence of larger and more frequent outbreaks, geographic expansion of endemic transmission, spread of the disease from urban to periurban and rural areas, and an increasing proportion of severe cases and deaths. An increased propensity to hyperendemicity, particularly in large urban areas, is also noted.

During 1996, a severe outbreak of dengue or DHF occurred in Delhi wherein about 10,252 cases and 423 deaths were reported. In 2006, India witnessed another outbreak with 12,317 cases and 184 deaths in 21 states. The initial epidemics in India were due to serotype 2 or 4. The dengue serotype 1 was seen as predominant serotype in Delhi during 2007–2010. Concurrent infection of chikungunya and dengue serotype 2 has been reported from Vellore and Delhi. Cyclic epidemics are increasing in frequency and in-country geographic expansion is reported in India due to deciduous dry and wet climatic zone with circulation of multiple virus serotypes. However, with improved case management, the case fatality has decreased from 3.3% in 1996 to 0.4% in 2010.

ETIOLOGY

Dengue virus (DENV) has at least four serotypes (1, 2, 3, and 4). These are antigenically very similar, but do not offer a complete cross-protection after infection by either one of them. Infections in human by a serotype will produce lifelong immunity against reinfection by the same serotype. Subsequent infection (secondary infection) by another serotype results in severe dengue. The severity of epidemics caused by serotype 1 has been reported to be maximum followed by types 2 and 3. Recent report from northwest India reported DENV-2 as the most common serotype with maximum proportion of severe cases. However, DENV-4 remains the most common serotype in circulation in Karnataka followed by DENV-2 and DENV-3. Coinfection with more than one serotype was seen in <10% cases.

EPIDEMIOLOGY

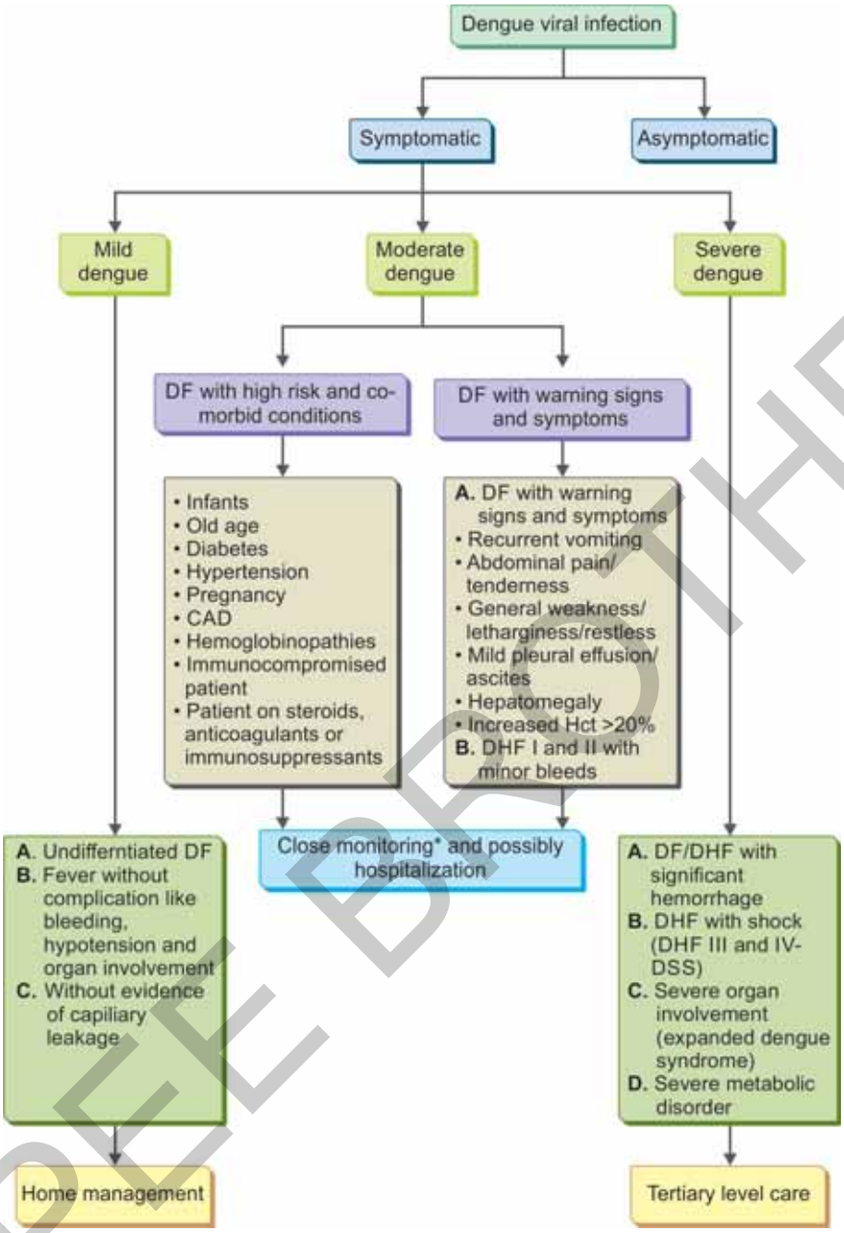
Vector

Aedes aegypti is the vector for dengue virus. Female mosquito bites the man during daytime. After feeding on a person with viremia, the female mosquito can transmit dengue immediately or after a period of 10–14 days (*extrinsic incubation period*). The extrinsic incubation period is a critical factor in successful transmission of the disease. A lower environmental temperature increases the extrinsic incubation period, which in turn, decreases the transmission. Once the mosquito becomes infective, it remains so till it dies.

The flight range of an adult *A. aegypti* mosquito is not >25–50 m in an urban environment. However, the vector can be transported by water, land, and air travel contributing to the transmission. For dengue transmission, the number of infected female mosquitoes per house is important. Usually this number is small, and, in an Indian epidemic, it was observed to be just 1 per household (*house index*). The minimum vector density, below which the dengue transmission ceases, is not known. The *A. aegypti* mosquito breeding is not necessarily related to the ambient temperature. The mosquito has been found at altitudes as high as 2,200 m above the sea level. Vectors must survive longer than the sum of the initial nonfeeding period after birth (usually 2 days) and the extrinsic incubation period to be able to infect another human. Longevity under natural conditions ranges from 8 days to 42 days. The eggs of *A. aegypti* can survive without water for a year.

An increase in resistance to commonly used insecticides is reported among *Aedes* from Southeast Asia. The common mechanisms of insecticide resistance include the following—(1) resistance of the target

Flowchart 1: Classification of dengue—WHO, 2015.



*Close monitoring: HCt, Plt, Hb, fluid intake/output, HR, RR, BP consciousness.
(DF: dengue fever; DHF: dengue hemorrhagic fever; CAD: coronary artery disease; DSS: dengue shock syndrome; Hct: hematocrit; Plt: platelet; Hb: hemoglobin; HR: heart rate, RR: respiratory rate; BP: blood pressure)
Source: National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. (2014). National guidelines for clinical management of dengue fever. [Online] Available from https://nvbdcp.gov.in/Doc/Dengue-National-Guidelines-2014.pdf [Last accessed October, 2021].

site of insecticidal action in mosquitoes through genetic modification, (2) metabolic resistance where resistant strains can detoxify or metabolize the insecticides, (3) penetration resistance to the insecticides through outer cuticle of mosquitoes, and (4) behavioral adaptation where mosquitoes develop mechanisms to evade contact with insecticides.

Host

People at all ages are susceptible to dengue. In Asians, disease is more severe in children. This is in contrast to America where infection mainly occurs in adults, which is generally mild. Severe dengue occurs at high frequency in (1) infants and (2) children having experienced a previous dengue infection. Other factors associated with increase host susceptibilities to severe disease include bronchial asthma; human immunodeficiency virus (HIV); certain human leukocyte antigen (HLA) types—HLA I (A04, A24, B0, B46), HLA II (DR1, DR4, DQ); polymorphisms in tumor necrosis factor-alpha (TNF-α); transforming growth factor-beta (TGF-β); vitamin D receptors; glucose-6-phosphate dehydrogenase deficiency, and mutations in mannose-binding lectin-2 gene.

Environmental Factors

In many tropical countries, a positive association between rainfall or larval density and dengue incidence has been documented. The vector survives best at temperature 16–30°C and humidity of 60–80%.

However, dengue epidemics have also been recorded in those areas where rainfall is unusually low. The transmission occurs only if the ambient temperature is above 16°C. Therefore, the transmission tends to decline when winter approaches. This is due to prolongation of extrinsic incubation period beyond the longevity of mosquito.

Transmission Risk Factors

When a member of a household is infected with dengue, other family members are at risk. Dengue spread is facilitated in any vector infested place where people congregate, such as schools, temples, cinema halls, offices, hospitals, factories, etc. In urban areas, the movement of infected people accounts for spread of virus than the movement of *Aedes* mosquito.

In Utero Transmission

Dengue infection of pregnant women may result in passive transfer of antidengue immunoglobulin G (IgG) to the fetus or a congenital infection. These infants with maternal antibody are at a higher risk of developing severe dengue and many develop DHF during primary exposure.

PATHOGENESIS

Dengue virus infects the peripheral blood mononuclear cells within a few days of infective mosquito bite. Two patterns of immune response follow—(1) *primary* and (2) *secondary* (*anamnestic*). Persons never previously infected with a flavivirus, nor immunized with a flavivirus vaccine (e.g., yellow fever, Japanese encephalitis), mount a primary IgM antibody response when infected with dengue virus, appearing within 2–3 days of defervescence and peaking at 2 weeks after the onset of symptoms. Antidengue IgG appears afterward. Individuals with immunity due to previous flavivirus infection or immunization mount a secondary (anamnestic) antibody response when infected with dengue virus. In secondary flavivirus infections, which account for most cases of severe dengue, the dominant immunoglobulin is IgG; the levels of IgM being much lower. A mechanism of immune enhancement or antibody dependent enhancement (ADE) is observed in dengue due to heterologous non-neutralizing antibodies. This is responsible for serious organ dysfunction and hemorrhagic disturbances, which can occur during secondary infection by a different serotype. This mechanism promotes binding of dengue virus to surface expressed Fc gamma (Fc_g) receptors on monocytes and macrophages, further promoting viral replication and spread. Thus, sequential rather than simultaneous exposure of different serotypes of dengue virus carry a higher chance of ADE resulting in serious disease. Thus, antibody against a strain of dengue virus does not protect from a different strain of virus. Rather, it may increase its capacity to multiply in human monocytes. The infected monocytes result in activation of cross-reactive $CD4^+$ and $CD8^+$ cytotoxic lymphocytes. Cytotoxic lymphocytes mediate release of cytokines resulting in plasma leakage and hemorrhage and are primarily responsible for host defense in dengue mediated via interferon-gamma. Recent studies have highlighted the role of HLA-linked protective role of CD8 lymphocytes. Researchers have found that certain phenotypes of HLA may cause hyporesponsiveness of interferon-γ response, thereby weakening the host response.

PATHOPHYSIOLOGY

Two main pathophysiological changes occur in dengue. These are—(1) *increased vascular permeability*, resulting in loss of plasma from the vascular compartment, hemoconcentration, low pulse pressure, and other signs of shock; and (2) disorder in the hemostasis involving thrombocytopenia, vascular changes, and coagulopathy.

Secondary dengue infection results in formation of immune complexes and activation of complement system. TNF-α, interferon, and interleukin-2 are elevated, and C1q, C3–C8, are depressed. As a result, vasoactive amines are released from the platelets. These cause massive release of water, electrolytes, and plasma proteins from the blood vessels and lead to hypovolemic shock.

Increased vascular permeability is mediated through the nitric oxide pathway.

Platelet defects are both quantitative and qualitative. Thus, a patient with a normal platelet count may still have a prolonged bleeding time. Maculopapular and petechial rashes are present. In these lesions, dengue antigen, IgM, and complement (C3) have been observed.

It may be noted that virus is usually not detectable in blood once shock manifests, though viral replication occurs in various organs.

CLINICAL FEATURES

Dengue infections have a wide clinical presentation. Following an incubation period of 3–7 days, the illness is characterized by three distinct phases—(1) febrile phase, (2) critical phase, and (3) phase of recovery.

Febrile Phase

This phase is characterized by a high-grade fever up to 104°F, abrupt in onset. Fever remains at the peak for 48–72 hours before it starts declining. It is accompanied with nonspecific constitutional symptoms, such as generalized myalgia, body ache, anorexia, nausea, vomiting, and headache. Parents may notice an erythematous rash, especially over the extremities. Infants with dengue usually have fever accompanied with gastrointestinal or nonspecific respiratory symptoms. There may be flushing of skin with compromised cutaneous circulation **(Fig. 2)**. Some children may have associated sore throat, or arthralgia. These features, by themselves, are however not sufficient enough to arrive at a diagnosis of dengue fever. Dengue should be strongly suspected, if above features are associated with mild hemorrhagic manifestations including petechial hemorrhages, mucosal bleeds, or a positive tourniquet test. Presence of tender hepatomegaly (without obvious icterus) strongly favors possibility of dengue infection. The febrile phase lasts for 2–3 days.

Complications

High fever in this phase can cause dehydration, febrile delirium, and febrile seizures in children <5 years of age. Febrile seizures, respiratory, and gastrointestinal manifestations are common in infants with dengue. Hepatomegaly is more frequently found in infants than in older children.

Critical Phase

Onset of the critical phase is closely linked to the time of defervescence that occurs by third day of illness. All children in defervescence phase need to be closely monitored for the *warning signs* as described earlier. Those manifesting with one or more of these signs are likely to enter the critical phase. Not all children with dengue infection enter

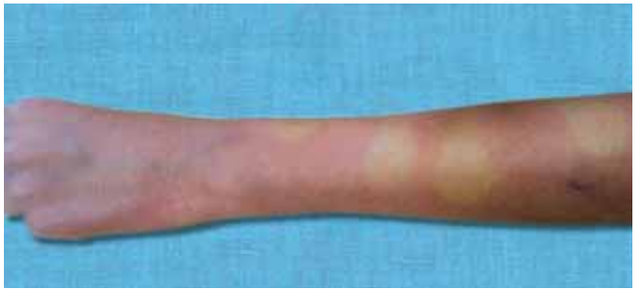


Fig. 2: Cutaneous flushing of forearm with blanching on applying pressure.

this phase. Many children improve progressively after defervescence (nonsevere dengue).

Critical phase is characterized by an increase in capillary permeability. This is preceded by a fall in the platelet count. Increased capillary permeability results in leakage of plasma into the third space. Clinically, this manifests as polyserositis, i.e., pleural effusion and ascites. Plasma leakage from the intravascular compartment into the third space results in hemoconcentration in the vascular bed, reflected by a rising Hct. Increase in Hct is directly proportional to the volume of plasma lost from the vascular compartment.

Epigastric discomfort, tenderness at right costal margin, and generalized abdominal pain are common. Liver becomes palpable. Petechiae may be present over extremities, axillae, face, and palate. Studies from India have reported the most frequent symptoms as fever, abdominal pain, headache, and vomiting.

Leakage of a significant volume of plasma leads to hypovolemia, hypoperfusion, and shock. Hypoperfusion may result in multiple end-organ impairment, metabolic acidosis, and disseminated intravascular coagulation (DIC). Consumption coagulopathy results in hemorrhage that may cause a fall in Hct. End-organ impairment manifests with hepatitis, myocarditis, or encephalitis. Children developing profound shock, severe hemorrhage, or multisystem involvement are at higher risk of mortality, and thus are said to be having *severe dengue infection*. These children need aggressive management. This phase lasts for 48 hours.

Recovery Phase (Plasma Reabsorption Phase)

Plasma starts coming back to the intravascular compartment, provided the patient survives the critical phase of plasma leakage and shock. Onset of this phase is characterized by an improvement in general well-being and appetite. Urine output improves and pain abdomen subsides. Though this is the phase of improvement, child should be monitored carefully for hypervolemia. Reabsorption of leaked plasma plus administration of excess intravenous (IV) fluid may result in fluid overload, pulmonary edema, and congestive heart failure, manifesting as dyspnea, tachycardia, and raised jugular venous pressure. Cardiovascular manifestations (bradycardia and arrhythmias) are also reported during this phase. Hct value either normalizes or may show a decline below normal. Platelet count starts improving. This phase lasts for 48–72 hours. Thus, most patients with dengue fever run a typical course of disease lasting from 7 to 10 days **(Fig. 3)**.

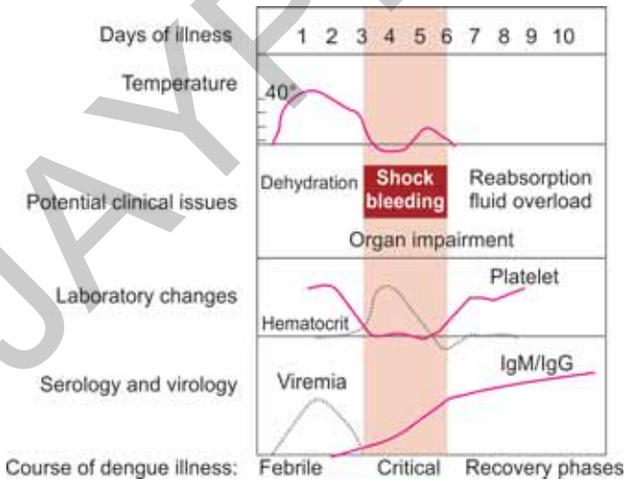


Fig. 3: The course of dengue illness. (Ig: immunoglobulin)
Source: Reproduced with permission of the publisher from Dengue, Guidelines for Treatment, Prevention Control. Geneva: WHO; 2009.

Severe Dengue

Children and adolescents with severe dengue have a more protracted course and recovery may take 10–14 days. Dengue shock is characterized by a narrow pulse pressure ≤20 mm Hg, cold extremities, delayed capillary refill time, weak pulse, and tachycardia. Skin becomes cool, blotchy, and congested. Typically, consciousness is not altered. Major bleeding can occur from gastrointestinal tract or brain. Organ impairment manifests as hepatic failure, renal failure, myocarditis, or encephalopathy. Atypical manifestations include acute inflammatory colitis, uveitis, myositis, Guillain–Barré syndrome, and Kawasaki disease.

Neurological manifestations are increasingly being reported in dengue infection commonly with DENV-2 and DENV-3 serotypes with an incidence varying from 0.5 to 21%. The neurological manifestations can result from direct virus-mediated action (neurotropism), postinfectious immune-mediated reaction or associated metabolic derangements in dengue infection. The spectrum of neurological manifestations varies from encephalopathy, encephalitis, aseptic meningitis, meningoencephalitis, stroke (hemorrhagic or ischemic stroke), acute disseminated encephalomyelitis, ataxia, Guillain–Barré syndrome, transverse myelitis, and myopathy. Dengue encephalopathy may be commonly associated with severe dengue or dengue shock syndrome, or with other metabolic abnormalities. Analysis of cerebrospinal fluid becomes important in suspected cases with neurological involvement in endemic areas. The leukocyte count in CSF may be normal in dengue encephalitis; however, it may yield positive results on immunoassays (specific IgM) and molecular tests (RT-PCR) to identify DENV and exclude other possible infectious causes. Neuroimaging may be normal or may show nonspecific changes in encephalitis, meningoencephalitis, and myelitis. Peripheral nervous system involvement is less frequently seen than central nervous system and usually presents later in the course of disease.

Notably, epidemiological studies have not found any correlation between platelet count and occurrence of bleeding manifestations or risk of mortality. The risk factors for mortality reported from adult studies include shock, hepatitis, renal failure, encephalopathy, and plasma leakage.

DIAGNOSIS

Hematological Tests

The clinical diagnosis is corroborated by raised Hct and thrombocytopenia:

- An Hct level rise of >20% is a sign of hemoconcentration and precedes shock. The Hct level should be monitored at least every 24 hours to facilitate early recognition of *warning signs* and every 3–4 hours in *severe dengue*.
- Thrombocytopenia occurs in up to 50% of children with dengue. Platelet counts of <100,000 cells/μL indicate onset of *critical phase* and typically occur before defervescence and the onset of shock. The platelet count should be monitored at least every 24 hours initially.
- The white blood cell count can be normal or show leukocytosis during initial phase. Leukopenia, often with lymphopenia, precedes thrombocytopenia and is observed near the end of the febrile phase of illness.

Biochemical Profile

Prothrombin time is prolonged. Activated partial thromboplastin time is prolonged. Low fibrinogen and elevated fibrin degradation product levels are signs of DIC. Hyponatremia is the most common electrolyte abnormality in critical phase. Metabolic acidosis and elevated blood urea are observed in those with shock. Serum glutamic pyruvic transaminase (SGPT) levels are elevated. Low serum albumin levels are a sign of hemoconcentration.

TABLE 1: Diagnostic tests for dengue fever.

Diagnostic method	*Timing of test (after disease onset)*	*Validity*
Virus isolation (culture)	1–5 days	++++
Genome detection (PCR)	1–5 days	++++
Antigen detection (NS1)	1–5 days	+++
Antibody detection (IgM)	After 5 days*	++
IgG (paired sera)**	Acute sera 1–5 days; convalescent sera after 15 days	+

*IgM positivity rates: by 3–5 days (50%), 5–7 days (80%), and 10 days (90%). IgM appears between 3 and 10 days and disappears by 2–3 months.
**IgG appears after 1–2 weeks and may persist for life.
(PCR: polymerase chain reaction; Ig: immunoglobulin)

Serodiagnosis

Serum specimens should be sent to the laboratory for serodiagnosis, polymerase chain reaction (PCR), and viral isolation. Because the signs and symptoms of dengue fever are nonspecific, attempting laboratory confirmation of dengue infection is important. Serodiagnosis is based on—(1) detection of viral nonstructural protein 1 (NS1) during initial illness; (2) detection of IgM antibodies to dengue; or (3) fourfold rise in dengue IgG in paired samples. **Table 1** outlines the desired timing of these tests for confirming the diagnosis. Laboratory criteria for definitive diagnosis include one or more of the following:

- Isolation of the dengue virus from serum, plasma, leukocytes, or autopsy samples
- Demonstration of dengue virus antigen in serum samples via enzyme immunoassay or in autopsy tissue via immunohistochemistry or immunofluorescence can be done. NS1 is a glycoprotein produced by the virus, which can be detected early, between 1st and 4th day of illness. It is specific and has a high sensitivity.
- Demonstration of a fourfold or greater change in reciprocal IgG or IgM antibody titers to one or more dengue virus antigens in paired serum samples. IgM antibody appears early in disease course, requires single sample, and is less cross-reactive to other flaviviruses. Thus, measurement of raised IgM appears to be most prudent when done after 5th day of illness. As per the NVBDCP, the laboratory test being followed is the IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA) for dengue virus, which captures the dengue-specific IgM by using antihuman IgM. There are quicker and cheaper rapid diagnostic test (RDT) kits available, which test the presence of anti-IgM or IgG or NS1 antigen. However, these kits carry a high false-positive rate and are not recommended by the WHO or under NVBDCP.
- Detection of viral genomic sequences in autopsy tissue, serum, or cerebral spinal fluid (CSF) samples via PCR.

Diagnostic kits for NS1 and MAC-ELISA can be procured from National Institute of Virology, Pune under NVBDCP. The Government of India has set up surveillance hospitals and apex referral laboratories for improved disease surveillance.

TREATMENT Dengue Fever

The mainstay of treatment is supportive therapy. Increased oral fluid intake is recommended to prevent dehydration. Supplementation with IV fluids may be necessary to prevent dehydration and significant hemoconcentration. Fever is managed with paracetamol. Aspirin and nonsteroidal anti-inflammatory drugs should be avoided as these drugs may worsen the bleeding tendency associated with some of these infections. Shock is managed with isotonic fluids. Packed cell transfusion is indicated in refractory shock or if there is significant bleeding.

Patients with known or suspected dengue fever should have their platelet count and Hct measured daily from the third day of illness until 1–2 days after defervescence. Patients with a rising Hct level or falling platelet count should be monitored more frequently. Management of dengue illness can be discussed in three steps:

Step 1: Overall assessment

Step 2: Diagnosis and severity assessment

Step 3: Categorizing into mild, moderate or severe dengue and treating accordingly

Overall Assessment

History and Examination

Emphasis on history should be on assessment of *warning signs*. Physical examination should concentrate on hemodynamic assessment, so as to determine the presence and extent of shock, confirming or detecting the warning signs, and checking for bleeding manifestations, abdominal tenderness, mental state, and hydration. Tourniquet test is a must.

Investigations

Initial investigations should include an Hct, WBC count, platelet count, and tests to confirm the diagnosis, as described in the section on laboratory diagnosis. In critical phase, additional tests need to be done and include liver function test, renal function test, chest X-ray, serum electrolytes, and ultrasound abdomen.

Diagnosis and Severity Assessment

Determine the phase of disease (febrile, critical, and recovery) and severity (nonsevere, severe) of dengue, as per criteria outlined earlier. The child will need admission if any of the following criteria is fulfilled:

- Presence of any of warning signs
- Signs and symptoms of hypotension
- Bleeding from any site
- Renal, hepatic, or central nervous system (CNS) involvement
- Pleural effusion or ascites
- Rising Hct
- Platelet count <50,000/mm^3
- High-risk age group—infants and old age

Categorize Patients in Mild, Moderate, and Severe Dengue (Table 2)

This step is aimed to place the patient in an appropriate group (mild, moderate, and severe) to decide on future course of action, as follows:

- *Mild:* Patients, who may be sent home
- *Moderate:* Patients needing close monitoring and hospitalization
- *Severe:* Patients requiring tertiary level care

Mild Dengue: Home Management

All children who are tolerating oral fluids, passing urine at least once in 6 hours, and not having any of the warning signs can be sent home. Following management needs to be advised:

- Encourage fluid intake; can give oral rehydration salt (ORS), fruit juice, etc. The parents should be advised to increase the amount of oral fluids to be given (e.g., 3–10 kg: 100 mL/kg and 10–20 kg: 75 mL/kg)
- Paracetamol (15 mg/kg/dose) if the child is uncomfortable because of fever. Avoid aspirin, ibuprofen, mefenamic acid, and nimesulide.
- Monitor at home for fluid intake, urine output, fever, obvious bleeding, and altered sensorium.
- Bring back if any of the above is present or the child develops any of the warning signs.

Parents of infants should be explained the danger signs before discharging them home. Tepid sponging for fever should be done as febrile convulsions may occur commonly in this age group. Breastfeeding should be encouraged and continued.

TABLE 2: Treatment of dengue.

Category	*Patient characteristics*	*Treatment*
Mild	Accepting orally, passing urine adequately and no warning signs*	*Home therapy:* Increased oral fluids, paracetamol
Moderate	• Warning signs* present • High risk-infants, old age, pregnancy • Comorbid conditions**	*Hospitalize:* • Monitor hematocrit, platelets, vitals • *Intravenous fluids:* Titrated as per hematocrit • If worsens, manage as severe dengue
Severe	• Severe bleeding • Severe shock • *Severe organ dysfunction:* Hepatic, CNS, heart, kidney • Severe metabolic disorder	*Intensive care:* • Monitor hematocrit, platelets, vitals • *Treatment of shock:* Normal saline bolus • Blood transfusion for severe bleeding or clinical worsening. Judicious use of platelets • Supportive treatment for organ failure • Watch for signs of fluid overload, and treat, if detected (oxygen 2, frusemide)

**Warning signs:* Abdominal pain, persistent vomiting, mucosal bleed, hepatomegaly, clinical fluid accumulation, lethargy, hemoconcentration, thrombocytopenia
**Comorbid conditions include hypertension, diabetes, thyroid illness, renal disease, hemoglobinopathy, hepatitis, and heart disease.

Moderate Dengue: Close Monitoring and Hospital Management

Any patient who fulfills the admission criteria should be admitted (as mentioned above). They may or may not have warning signs. A baseline Hct is measured and monitoring is started. In cases where no warning signs are present, patients should be started on maintenance fluids with isotonic fluid. If patient shows signs of mild dehydration, a correction of 50 mL/kg (<12 months) and 30 mL/kg (>12 months) is added to main fluid. At all times, clinical parameters are closely monitored and correlated with Hct to guide further fluid therapy. For those who present with warning signs, the following is advised **(Flowchart 2)**:

- Start isotonic IV fluids (normal saline or Ringer's lactate) at 6 mL/kg/h for 1–2 hours
- Reassess Hct and clinical status:
  - If improvement occurs, decrease to 3 mL/kg/h for 2–4 hours, and then continue with 1.5 mL/kg/h for 2–4 hours
  - If clinical status worsens or Hct rises, increase rate of fluids to 10 mL/kg/h for 1–2 hours
- Reassess clinical status, repeat Hct, and review fluid infusion rates, till the child is better
  - If the child improves, maintain minimum IV fluids at 1.5 mL/kg/h for 24–48 hours. Stop fluids when child demands and accepts adequate oral fluids and food.
  - Those who worsen or develop profound shock, bleeding or multisystem involvement, manage as in **Flowchart 3**.

Severe Dengue: Tertiary Level Care

Emergency treatment is required in children with severe dengue or those in critical phase as follows:

- Obtain Hct, blood count, and other organ function tests, as indicated
- *Compensated shock:* This stage is characterized by low systolic blood pressure, narrow pulse pressure (<20 mm Hg), and rise in hematocrit (>20%). In these children, fluid resuscitation is started at 10–20 mL/kg/h, and further directed as per **Flowchart 3**.
- *Hypotensive shock:* Administer isotonic fluid bolus 20 mL/kg in 15 minutes. For further management, follow the algorithm depicted in **Flowchart 4**. Colloids may be needed in refractory shock. Colloids can be gelatin- or starch-based. They carry theoretical risk of impaired coagulation and allergic reactions. They should be infused slowly with strict monitoring for signs of fluid overload.
- *Hemorrhagic complications:* Suspect severe bleeding if there is an unexplained fall in Hct, refractory shock not responding to 40–60 mL/kg of fluid, and persistent or worsening metabolic acidosis. Packed cell transfusion 10 mL/kg over 2–3 hours can be lifesaving in these children. There is not much evidence for platelet transfusion or fresh frozen plasma for severe bleeding. Platelet transfusions should not be used prophylactically. Its use has neither shown to prevent progression to severe bleeding nor does it shorten the bleeding time and may instead be associated with severe side effects. Platelet transfusion should be restricted to cases with severe bleeding or when platelet counts are below 10,000/mm^3. Platelets obtained by single donor apheresis are preferred as they raise the platelet count by 30,000–50,000 as compared to random donor platelets, which result in rise by 5,000–10,000 per unit.
- *Monitoring:* This essentially remains the basic prerequisite for treating children with severe dengue, in an emergency setting.
  - Monitor vital signs and peripheral perfusion 1–4 hourly unless patient is out of critical phase. Monitor Hct before and after fluid replacement, then 6–12 hourly.
  - Monitor blood glucose and other organ dysfunction both clinically and biochemically.
  - A typical monitoring chart for dengue fever should record the following: body temperature, heart rate, blood pressure, pulse volume, capillary refill time, abdominal pain, appetite, abdominal pain, vomiting, bleeding, and sensorium.

Treatment of Fluid Overload

A patient with dengue can have fluid overload due to excessive or rapidly transfused IV fluids, use of hypotonic fluids, and inappropriate use of fresh frozen plasma or platelets. Another important reason is continuation of IV fluids even during the phase of plasma reabsorption and recovery.

These children may present with features of pulmonary edema or congestive heart failure. Following management is suggested:

- Oxygen therapy
- Discontinuation or reduction of IV fluids
- Frusemide 0.1–0.5 mg/kg/dose once or twice daily, maintaining serum potassium
- Look for occult hemorrhage and transfuse packed cells

Management of Other Complications

Encephalopathy in dengue may result due to dengue encephalitis, intracranial bleeding, electrolyte disturbances, occlusion due to DIC or hepatic failure. Appropriate diagnosis for cause and specific management should be instituted. Cardiac involvement may be seen during shock or during convalescence, which may manifest as arrhythmias or heart failure.

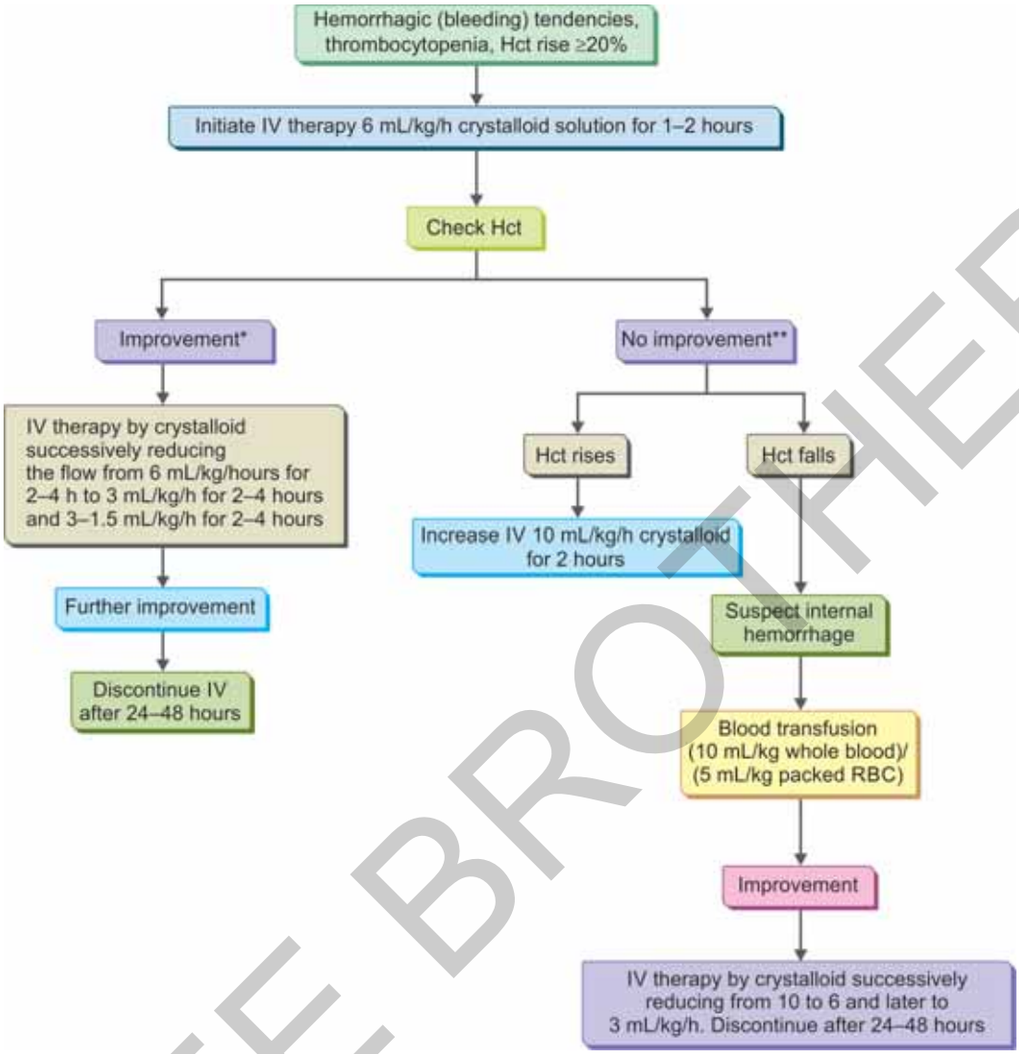
Criteria for Discharge

Patient should be discharged only if he has been afebrile for at least 24 hours, passing urine normally, having improved appetite, and has no respiratory distress. His laboratory parameters should show a stable Hct and platelet count of >50,000/mm^3.

PREVENTION AND CONTROL

Aedes aegypti should be the main target of surveillance and control. As per the WHO report on neglected tropical diseases, the global target is to reduce the case fatality from 0.8% in 2020 to 0% by 2030. The NVBDCP was launched in 2003, which extended vector control

Flowchart 2: Management of moderate dengue.



(Hct: hematocrit; RBC: red blood cell)
Source: National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. (2014). National guidelines for clinical management of dengue fever. [Online] Available from https://nvbdcp.gov.in/Doc/Dengue-National-Guidelines-2014.pdf [Last accessed October, 2021].

services for dengue and Japanese encephalitis. A mid-term plan was approved in 2011 to enhance the country's capacity to control dengue. The activities targeted against dengue include:

- Increasing diagnostic facilities. Introduction of ELISA-based NS1 antigen for diagnosis of dengue early in disease.
- Monitoring and surveillance of vector control
- Capacity building of medical health personnel
- Increasing social mobilization through information, education, and communication (IEC) activities for vector control.

Surveillance

Disease Surveillance

Tracking the number of suspected and confirmed infected human cases. It also includes recording the circulating serotypes of dengue and the number of deaths from dengue.

Vector Surveillance

Tracking mosquito populations in areas of potential risk: Mainly two indices are used for measuring the vector density. These are—(1) *house index* and (2) *Breteau index*. House index is defined as the percentage of houses positive for the larvae; and Breteau index as the number of containers positive for the larvae per 100 houses. These indices measure larval infestation rather than adult mosquito density. Epidemic spread of *Aedes* has been reported with *house index* as low as 1% in Indian settings.

Monitoring Behavioral Impact

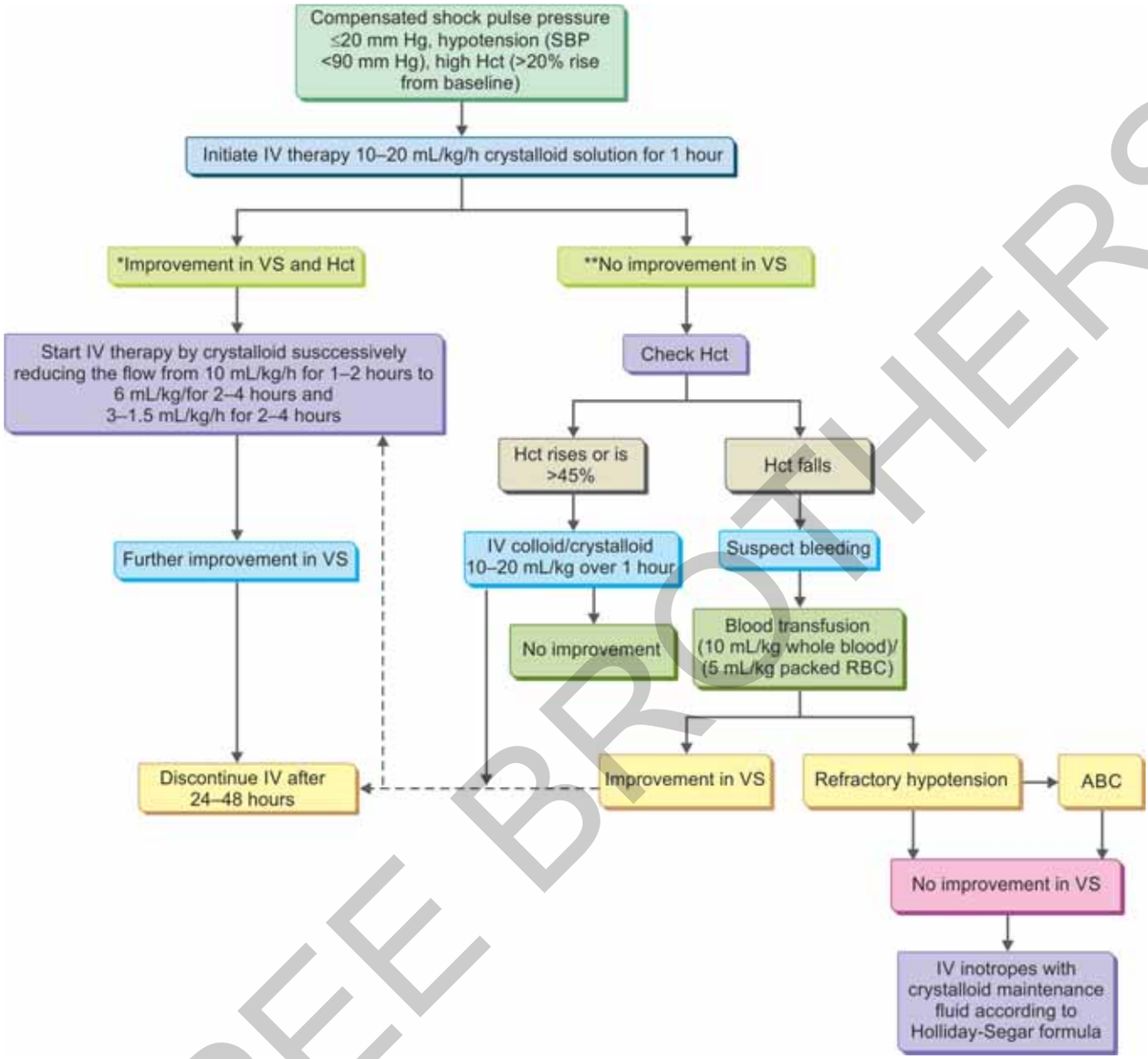
Communication for behavioral impact (COMBI) is a methodological process where communication interventions are used to help a community adopt healthy behaviors aimed to reduce mosquito multiplication and spread. The surveillance is done by observing whether such behaviors are adopted and sustained by the community.

Vector Control

The following measures have been advocated as Government advisory to contain vector spread like:

- *Environmental modification:* This includes long-lasting physical transformation of *Aedes* mosquitos' habitats. Sprays of larvicides are recommended in high-risk localities. Large tanks with taps

Flowchart 3: Algorithm for fluid management in compensated shock.



(SBP: systolic blood pressure; VS: vital signs; Hct: hematocrit; RBC: red blood cell; ABC: airway, breathing, circulation)
Source: National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. (2014). National guidelines for clinical management of dengue fever. [Online] Available from https://nvbdcp.gov.in/Doc/Dengue-National-Guidelines-2014.pdf [Last accessed October, 2021].

should be kept covered. Management of roof tops, porticos, and sunshades to be encouraged.

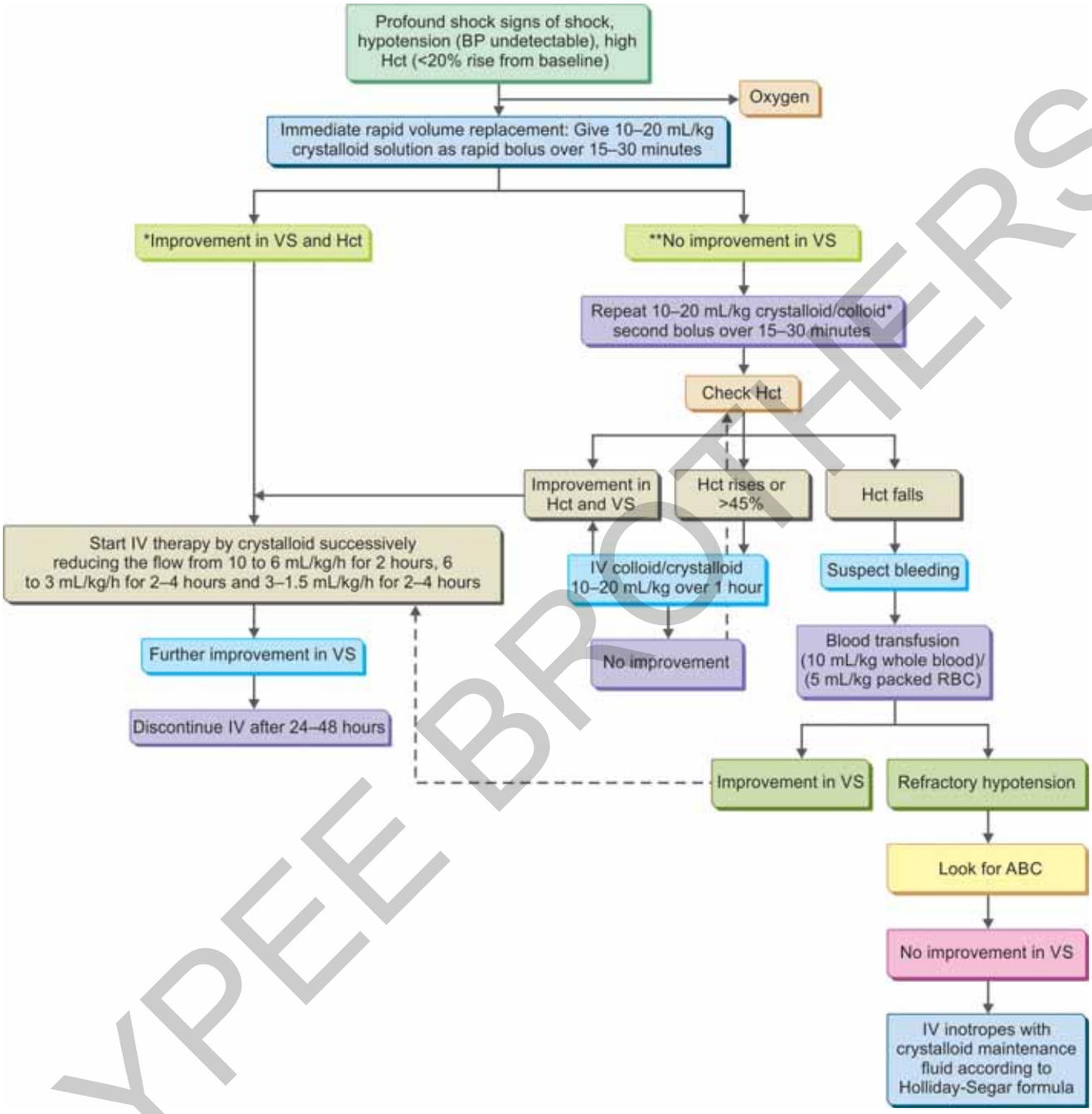
- *Environmental manipulation:* Sensitize and involve the community for detection of *Aedes* breeding places and their elimination. All objects that may collect water (old tyres, broken jars, empty tins, and bottles) should be disposed off. Water should be changed routinely in water coolers, flower vases, and overhead tanks. Coolers, if not in use, should be drained and mopped dry.
- *Changes in human habitations:* Human habitations are to be made mosquito proof by use of mesh on doors/windows. Health education should be provided regularly in schools and through mass media.

Biological and Chemical Control

Use of chemical larvicides, such as *Abate*®, in big breeding containers has been found useful. Aerosol space spray during daytime may be another option in high-density areas. Temephos is an effective larvicide when used in a concentration of 1 PPM. This dose has been found safe with low mammalian toxicity. The chemicals that are effective as adulticides for *Aedes* include pyrethrum and malathion. Pyrethrum is used as indoor spray in concentration of 0.1–0.2% at the rate of 30–60 mL/1,000 cubic feet (commercial ready to use preparations are diluted with kerosene). Malathion is used for fogging or ultralow volume sprays.

Use of larvivorous fish in ornamental tanks, fountains, or biocides can kill the larval stages. In recent years, interest in mosquito-killing (entomopathogenic) fungi is reviving, mainly due to continuous and increasing levels of insecticide resistance and increasing global risk of mosquito-borne diseases. Particular focus is on species belonging to the genera *Lagenidium, Coelomomyces, Entomophthora, Culicinomyces, Beauveria, and Metarhizium*. *Bacillus thuringiensis* serotype H-14 (Bt H-14), an endotoxin producing bacteria, has also been found useful in vector control.

Flowchart 4: Algorithm for fluid management in hypotensive decompensated shock.



(BP: blood pressure; VS: vital signs; Hct: hematocrit; RBC: red blood cell; ABC: airway, breathing, circulation)
Source: National Vector Borne Disease Control Programme, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India. (2014). National guidelines for clinical management of dengue fever. [Online] Available from https://nvbdcp.gov.in/Doc/Dengue-National-Guidelines-2014.pdf [Last accessed October, 2021].

There has been recent research exploring the control of *Aedes* mosquito by genetically engineering male insects, which carry dominant lethal gene (RIDL) at both pupa and adult stages.

Vaccine Development

A live attenuated tetravalent dengue vaccine (CYD-TDV) has been developed which contains four dengue virus with expression of dengue premembrane and envelope protein and nonstructural and capsid protein of yellow fever strain (YF-17D). The vaccine is administered as three-dose schedule and has shown good protection against dengue serotype 1, 3, and 4. The vaccine is still under multicentric phase III trials. Early results following 3 years post vaccination have shown a 50–58% reduction in risk for hospitalization among vaccines. Several research groups are successfully exploring an infectious clone technology for the development of a dengue vaccine. The Chimeri VaxTM system, originally developed to construct JE vaccine, has now been applied to dengue viruses. This vaccine was shown to be safe and immunogenic in a monkey study. Another approach is based on the use of a dengue type 4 mutant containing a deletion for the construction of a dengue chimeric vaccine. Phase I clinical trials of a

deletion mutant carried out in adult humans showed good safety and immunogenicity.

In India, the yeast, *Pichia pastoris,* has been used to develop a noninfectious dengue virus-2 virus-like particle consisting of viral envelope protein using recombinant DNA technology. The vaccine is under trial.

IN A NUTSHELL

1. Dengue is spread by *Aedes* mosquito, which multiples in collections of stagnated water.
2. Four different serotypes of virus exist. Antibody against one serotype does not confer protection against another. Rather, the illness is more severe following secondary infection in a child sensitized against a different serotype earlier.
3. Increased capillary permeability and coagulopathy chiefly contribute to disease manifestations. Thrombocytopenia occurs both due to bone marrow suppression and immune-mediated destruction.
4. Clinical presentation consists of a biphasic fever, myalgia, arthralgia, and hemorrhagic manifestations, lasting over 3–7 days. The most vulnerable stage is soon after defervescence (critical phase) characterized by increased capillary permeability.
5. Serological diagnosis is possible by detecting nonstructural (NS) antigen 1 between 2 and 5 days, detection of IgM antibodies between 5 and 10 days, or fourfold rise in IgG antibodies after 7–10 days.
6. Children with *warning signs* should be hospitalized. Those with severe shock, severe bleeding, and organ involvement need management in intensive care unit (ICU) setting.
7. Fluid therapy is the mainstay of treatment. Crystalloid is the fluid of choice during resuscitation. Best guide to fluid therapy is Hct.

MORE ON THIS TOPIC

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31.20 Chikungunya Fever

Rajniti Prasad

Chikungunya, a viral fever, is caused by an alphavirus [chikungunya virus (CHIKV)] and spread by bite of an infected *Aedes aegypti* mosquito. The disease was first described in 1955 following an outbreak on the Makonde plateau. The name derives from kungunyala, meaning *to dry up or become contorted.* Although primarily African and zoonotic disease, non-African large urban outbreaks have been reported, which is transmitted by the same vectors as those of dengue viruses. Since then, CHIKV has caused numerous outbreaks and epidemics in both Africa and Southeast Asia, affecting many children.

CHIKUNGUNYA VIRUS

Chikungunya virus, a positive strand, enveloped RNA (ribonucleic acid) virus, is a member of the alphavirus of *Togaviridae* family. It is closely related to O'nyong-nyong viruses. Three distinct phylogroups were reported on the basis of E1 envelope glycoprotein gene sequence—first contained all isolates from West Africa, second comprised all Central, Southern and Eastern African (CSEA) strains, and third isolates from Asia. Complete genomic sequence of CHIKV has 11,805 nucleotides in length. Coding sequences consist of two

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- A MUST for every postgraduate student and practicing pediatrician in India.

Piyush Gupta MD FAMS is a renowned academician, teacher, researcher, author and editor; he has published more than 300 papers, 400 book chapters, and edited/authored 40 books, including *Textbook of Pediatrics, Clinical Methods in Pediatrics, Essential Pediatric Nursing, IAP Textbook of Pediatrics, Principles of Medical Education,* and *How to Write a Thesis.* He has served as Editor-in-Chief of 'Indian Pediatrics,' (official journal of the Indian Academy of Pediatrics) for 6 years. He has been conferred fellowships by the Royal College of Paediatrics, UK; Indian Academy of Pediatrics; National Neonatology Forum, India; National Academy of Medical Sciences, India; and awarded by the American Academy of Pediatrics for his work on micronutrients. His major initiatives include workshops on thesis and scientific paper writing; and increasing awareness for practicing rational management of diarrhea and pneumonia in children. He has served as technical expert/advisor to the Government of India, World Health Organization (WHO), the United Nations Children's Fund (UNICEF), and the Indian Council of Medical Research (ICMR). He has delivered 34 orations, including the prestigious KL Wig Oration in the field of Medical Education in India. He has served as the Joint Secretary of South Asia Pediatrics Association. He is serving on the editorial board of several national and international journals. He has been awarded as the *National Teacher of Excellence* by the Vice-President of India. In 2021, he served as the National President of Indian Academy of Pediatrics.

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Printed in India

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ISBN 978-93-5465-121-2